REMARKS

Claims 1-12 and 14-28 are pending in the current application. In an office action dated September 8, 2006, the Examiner rejected claims 1-12 and 14-28 under 35 U.S.C. § 101, rejected claims 15-19 under 35 U.S.C. § 112, rejected claims 1-4, 7-8, 10-11, and 14-17 under 35 U.S.C. § 103(a) as being unpatentable over Larson et al., "Calculus with Analytic Geometry" ("Larson") in view of Schadt et al., Journal of Cellular Biochemistry, Volume 84, Issue S37, pp. 120-125 ("Schadt"), rejected claims 20-23 and 26-27 under 35 U.S.C. § 103(a) as being unpatentable over Larson in view of Schadt and further in view of a website: http://web.archive.org/web/20021008184825/http://www.s2.chalmers.se/~agrell/hpercues ("Chalmers"), rejected claims 1, 5, 6, 8, 9, 14, 18, and 19 under 35 U.S.C. § 103(a) as being unpatentable over Larson and Schadt in further view of Fredman, "Discrete Mathematics," volume 11, 1975 pp 29-35 ("Fredman"), and rejected claims 20, 24, and 25 under 35 U.S.C. § 103(a) being unpatentable over Larson and Schadt in further view of Fredman. In the above amendment, Applicants' representative has amended claims 1, 14-19, and 20 to address the Examiner's 35 U.S.C. § 101 and 35 U.S.C. § 112 rejection, although Applicants' representative does not believe the Examiner's 35 U.S.C. § 101 rejections are well founded or justified, as discussed below. Applicants' representative respectfully traverses the 35 U.S.C. § 103(a) rejections of claims 1-12 and 14-28.

First, Applicants' representative notes that Schadt, cited by the Examiner in the above-noted 35 U.S.C. § 103(a) rejections, states:

> It is well known that the comparison of gene expression results across experiments relies crucially on having an effective normalization scheme. (Schadt, page 120)
>
> Normalizing multiple probe arrays to allow direct array-to-array comparisons presents one of the greatest challenges in expression array data analysis. (Schadt, page 122)
>
> To address these problems, we have developed an invariant difference selection algorithm (IDS) that chooses a subset of PM/MM intensity differences to serve as the basis for fitting a normalization relation. (Schadt, page 123)

Moreover, beginning on line 8 of page 7 and extending to line 2 of page 10, a very clear and detailed discussion of why data normalization is of critical importance is provided,

with reference to Figures 8 and 9. It is difficult to imagine that anyone familiar with microarrays and microarray-data acquisition and analysis would have any doubt that a method for selecting a set of normalization data points is useful, tangible, and produces a concrete result. The Examiner states:

> The instant claims do not include any tangible result. A tangible requirement that the claim must set forth a practical application of the algorithm to produce a real-world result. While the claims are directed to a method, system, or computer product of an algorithm used to make paths between related strings, there is no tangible means of visualizing or displaying the output. Thus the instant claims do not include any tangible result.

Applicants' representative cannot find any reference to making "paths between related strings" in the current claims, and does not know to what the Examiner is referring. A set of normalizing data points is a perfectly tangible result, as well explained in the current application and in Schadt. A set of normalization data points is the basis for determining and applying a normalization curve or curves to multiple microarray data sets, so that the multiple microarray data sets can be interpreted relative to one another. A set of normalization data points is a set of calculated values used in a data-normalization process, without which microarray data from multiple-microarray experiments would be essentially useless. Applicants' representative cannot understand how the statement "there is no tangible means of visualizing or displaying the output" has any relation to the copious quotations that preceded it. Moreover, visualizing and displaying a set of normalization data points in not the point of the embodiments of the invention to which the current claims are directed. Instead, normalization data points are used to normalize microarray data. Were it the point of the of the embodiments of the invention to which the current claims are directed, it would be quite straightforward for a selected set of normalization data points to be displayed, graphically, textually, or in any of many other ways.

In short, Applicants' representative cannot understand the logic of the Examiner's 35 U.S.C. § 101 rejections, and does not feel that these rejections are well founded or justified. However, in the interest of furthering prosecution, Applicants' representative has amended claims 1, 14, and 20 to avoid further 35 U.S.C. § 101 rejections.

Similarly, Applicants' representative cannot understand the 35 U.S.C. § 103(a) rejections of claims 1-12 and 14-28. Larsen is unrelated to the subject matter to which the current claims are directed. The portion of Larsen cited by the Examiner is an introductory text on Cartesian space, vectors, and direction cosines. This material falls into the general topic of continuous mathematics, while, by contrast, the current application is related to discrete mathematics. As one small example of the inapplicability of Larsen to the current subject matter, the step of claim 1 "determining one or more order-preserving sequences of data points within the n-dimensional data-point space" involves selecting discrete points from a discrete-point space that can be ordered according to some ordering criteria. This is an area of discrete mathematics referred to as fully-ordered sets and partially-ordered sets. Lattices and set theory are other topics in discrete mathematics related to order-preserving sets. In order to select an order-preserving sequence of points, an ordering function must be defined, as well as the set of points from which an order-preserving sequence is to be selected. Larsen discusses or suggests nothing of the sort. A continuous function, such as a plane or line in Cartesian space, contains an infinite set of points, and, depending on how the ordering function is defined, would generally contain an infinite number of order-preserving points or most geometrically based ordering functions. Infinite sets are not useful for data normalization, because they are, obviously, computationally intractable.

The Examiner states that Figures 14.1, 14.4, and 14.6 on pages 785-787 of Larsen illustrate an order-preserving sequence. They do not, and these figures are not related to the current disclosure. Instead, they show an octant of Cartesian space, application of the Pythagorean Theorem, and the notation for a vector in Cartesian space, as clearly stated by Larson. Larsen does not teach, mention, or suggest anything at all concerning order-preserving sequences.

The Examiner states that the "rectangular solid is interpreted to be the longest order preserving sequence of the data points." First of all, there are no data points shown. Second, in a continuous space, most all order-preserving sequences that one can postulate contain an infinite number of points. The notion of a longest order preserving sequence in a continuous space makes little sense. Third, while it might be possible to

define an ordering function that would order all of the points in a rectangular solid into an order-preserving sequence, that ordering function is decidedly non-trivial, and nothing even remotely related to such an ordering of points is disclosed in Larson. For example, if the ordering function were selected to be the distance of points from the origin or from the *xy*-plane, or any other simple geometric distance function, there would be an infinite number of points in the rectangular solid with the same distance-metric value, and any line through the solid in which points were ordered by the distance function would contain an infinite number of points. There is no way to compare the sizes of such infinite sets in order to choose a longest order-preserving sequence of points.

The Examiner states that the "rectangular solid in Figure 14.1 of Larson et al illustrates a situation where data points are ordered and traversed in all three directions in order to find greatest metric sums based on changes in each of the three dimensions." This statement makes absolutely no sense. First, there are no data points listed, shown, or discussed in Figure 14.1. Figure 14.1 is intended to illustrate the positive octant of a Cartesian coordinate space. Second, Figure 14.1 does not show any kind of traversal or ordering. None is mentioned in Larsen. Third, there are an infinite number of directions in Cartesian space, not just three. Fourth, there is no mention, illustration, or suggestion in Figure 14.1, or in the text of Larsen referring to Figure 14.1, of computing sums based on changes, of changes, or of anything else mentioned by the Examiner in the above-quoted statement.

The Examiner states that the "method of finding order-preserving sequences of data points in the instant applications involves iteration(s) of determining traces of points in the same octant as the point before it with each subsequent point determining its own coordinate system." The statement makes no sense grammatically, makes no sense mathematically, is not reflected in the claim language, and is nowhere described in the current application. The current application does use a three-dimensional, abstract example in Figures 11A-C to illustrate order-preserving sequences. This is simply an abstract example, and is not at all described by the above-quoted statement. For computing normalization data points, the dimensions are data sets, not dimensions of a Cartesian space, as shown in Figure 13 and discussed at length in the

current application.

The Examiner states that "there is no guidance in the original disclosure as to how to calculate 'greatest sum of weights.'" The current disclosure provides a C++ implementation of a LOPS-based embodiment of the currently claimed methods, and includes, on lines 16-22 of page 44, a precise indication of how the C++ implementation can be slightly varied to implement a HOPS-based embodiment of the currently claimed methods, which involves sums of weights.

Chalmers is also unrelated to the subject matter to which the current application is directed. While 2-dimensional renderings of hyper-dimensional mathematical objects are fascinating and beautiful, they have nothing to do with order-preserving sequences and selection of normalizing data points. While Fredman's textbook on discrete mathematics is quite related, topically, to the current subject matter, bounds and limits of order-preserving sequences have nothing whatsoever to do with the thresholding techniques discussed in the current application and current claims. Fredman undoubtedly discusses the upper and lower bounds of order-preserving sequences, greatest lower bounds and least upper bounds, and other such topics with which discrete mathematics is concerned, but such bounds, useful in discussing, characterizing, and crafting proofs with regard to order-preserving sequences, have nothing at all to do with selecting data points within a threshold value of an order-preserving sequence of data points.

Of the four cited references, only Schadt is closely related to the subject matter of the current claims. In fact, Schadt is quite relevant. Schadt states, on page 123:

> To address these problems, we have developed an invariant difference selection algorithm (IDS) that chooses a subset of PM/MM intensity differences to serve as the basis for fitting a normalization relation. A set of probes are said to be invariant if the ordering of these probes according to the PM/MM differences in the experiment array, is the same as that in the baseline array.

However, Schadt then states, also on page 123:

> Although the maximal invariant set can be computed using a dynamic programming algorithm (not presented), the resulting set is typically too small to form a reliable normalization curve.

In other words, Schadt rejects the approach disclosed in the current application, and

explicitly states that Schadt does not disclose a method for computing such a set. Instead, Schadt uses a simple linear interpolation and difference-threshold technique, expressed in the equations on page 123, to try to approximate an invariant set. The difference metric involves an absolute value, indicating that it is a scalar value, such as a distance, rather than a directional value, and therefore cannot be used to select an order-preserving sequence with respect to rank, since ranks below and above a selected rank reference point would have an identical difference metric computed by Schadt.

The current invention, unlike Schadt, does involve computing order-preserving sequence, as clearly claimed in the independent claims, as shown in the C++ implementation included in the current application, and as discussed, at length, in the current application, including the discussion that refers to Figures 12, 13, and 14A-K. The current application discloses efficient computational techniques to allow such order-preserving sets to be efficiently computed, for useful application in microarray data analysis, and ordering functions that result in adequately-sized normalization sets even in higher-dimensional cases. Please note that Schadt indicates, in the above quite, that normalization sets produced for even a 2-dimensional case by the method Schadt rejected would be insufficient. By contrast, the currently claimed methods do provide for reasonably sized normalization sets.

In summary, of the four references cited by the Examiner, only Schadt is remotely related to the currently claimed methods and system. The Examiner's choice of references, and attempt to interpret cited sections of Larsen and Fredman, appears to Applicants' representative to indicate lack of familiarity, on the part of the Examiner, with computing, mathematics, and the contents of the current application. The current application is computational in nature, and Applicants' representative can well understand that the current application would be formidable reading for those without a background in computing. Applicants' representative would be most happy to discuss the current application with the Examiner in a telephone interview, and explain the disclosure and provide sufficient background information to understand the disclosure. Applicants' representative would also be happy to provide direction on textbooks in computing and discrete mathematics that would be useful for acquiring sufficient background to read and

understand the current application. Alternatively, Applicants' representative would respectfully suggest that the current application might be transferred to a quantitative art group, such as a computing or mathematical-computing art group, where Examiners have more familiarity with the subject matter of the current application.

In Applicant's representative's opinion, all of the claims remaining in the current application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,
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